

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/028506 A1

(51) International Patent Classification⁷: **A61K 9/16**,
9/20, 31/216

409, Sector-20, 166020 Chandigarh (IN). MALIK, Rajiv
[IN/AT]; Haus 13/4, Unterer Schreiberweg, A-1190 Wien
(AT).

(21) International Application Number:
PCT/IB2003/004162

(22) International Filing Date:
24 September 2003 (24.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
961/DEL/2002 24 September 2002 (24.09.2002) IN

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— with international search report

(71) Applicants (*for all designated States except US*): RAN-BAXY LABORATORIES LIMITED [IN/IN]; 19, Nehru Place, 110019 New Delhi, Delhi (IN). ROY, Sunilendu, Bhushan [IN/IN]; Bungalow # 7, Row House, Lokpuram, Thane (West), 400601 Mumbai, Maharashtra (IN).
(72) Inventors; and
(75) Inventors/Applicants (*for US only*): MIRIYALA, Gowri, Shankar [IN/IN]; 74, Asiad Village, 110049 New Delhi, Delhi (IN). SINGLA, Ajay, Kumar [IN/IN]; House No.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ORAL PHARMACEUTICAL COMPOSITIONS OF FENOFIBRATE HAVING HIGH BIOAVAILABILITY

(57) Abstract: The present invention relates to oral pharmaceutical compositions of fenofibrate having high bioavailability with improved dissolution and methods for providing the pharmaceutical compositions. The oral pharmaceutical composition of fenofibrate include an inert hydro-insoluble carrier having one or more one layers that include fenofibrate in a micronized form, one or more hydrophilic polymers, and one or more surfactants. The composition may have a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.



WO 2004/028506 A1

ORAL PHARMACEUTICAL COMPOSITIONS OF FENOFIBRATE HAVING HIGH BIOAVAILABILITY

This application claims priority from Indian Application No. 961/DEL/2002 filed on
5 September 24, 2002.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to oral pharmaceutical compositions of fenofibrate having high bioavailability with improved dissolution and methods for preparing the pharmaceutical compositions.

10 BACKGROUND OF THE INVENTION

Fenofibrate, 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester, belongs to the family of fibrates or fibric acid derivatives. It is commercially available as oral capsules containing micronized fenofibrate in the strengths of 67 mg, 134 mg and 200 mg. Fenofibrate is indicated as an adjunctive therapy to diet for the
15 treatment for adult patients with very high elevations of serum triglyceride levels who are at risk of pancreatitis and who do not respond adequately to dietary control. It is particularly useful for the treatment of adult endogenous hyperlipidemia, hypercholesterolemia and hypertriglyceridemia.

Fenofibrate is practically insoluble in water and exhibits a low rate of dissolution in
20 aqueous media that results in inadequate bioavailability after oral ingestion. This low rate of dissolution of fenofibrate in aqueous media also is found in gastrointestinal fluids. Several methods of increasing the rate of dissolution of drugs having low solubility in water and other aqueous media have been disclosed in the prior art.

U.S. Patent No. 4,895,726 discloses a fenofibrate composition in which fenofibrate is
25 co-micronized with a surfactant to improve the solubility of the fenofibrate. This patent emphasizes that co-micronizing fenofibrate with a solid surfactant improves fenofibrate bioavailability to a much greater extent than either by adding a surfactant to micronized fenofibrate or intimately mixing fenofibrate and surfactant, micronized separately. In order to further improve the solubility and bioavailability of fenofibrate, U.S. Patent No. 6,074,670
30 discloses attaining this objective by spraying a suspension of the active pharmaceutical ingredient on a hydro-soluble carrier. U.S. Patent No. 6,277,405 discloses an immediate release fenofibrate composition that includes an inert hydro-soluble carrier covered with at

least one layer containing fenofibrate in a micronized form having a particle size less than 20 μm , a hydrophilic polymer, and an optional surfactant.

SUMMARY OF THE INVENTION

5 In one general aspect there is provided an immediate release fenofibrate composition comprising an inert hydro-insoluble carrier with at least one layer containing fenofibrate in a micronized form, a hydrophilic polymer and a surfactant; and optionally one or several outer phases or layers.

10 In another general aspect there is provided an oral pharmaceutical composition of fenofibrate that includes an inert hydro-insoluble carrier having one or more layers that include fenofibrate in a micronized form, one or more hydrophilic polymers, and one or more surfactants.

Embodiments of the composition may include one or more of the following features. For example, the composition may further include two or more outer phases or layers. The two or more outer phases or layers may include one or more of fenofibrate in a micronized
15 form, one or more hydrophilic polymers, and one or more surfactants.

The composition may have a dissolution of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes, and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of
20 Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and more particularly, less than or equal to about 10 microns. The micronized fenofibrate may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

25 The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch. The hydro-insoluble carrier may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

The hydrophilic polymer may be one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and gelatin. The hydrophilic polymer may be present in an amount of from about 10% w/w to about 45% w/w
30 of the composition.

The surfactant may be one or more of sodium lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about
5 0.5% w/w to about 3.0% w/w of the composition.

The composition may further include one or more pharmaceutically acceptable excipients that include disintegrants, binders, fillers, glidants, lubricants, colorants, wetting agents, buffers, and coatings. The disintegrant may be one or more of croscarmellose sodium, cross-linked polyvinyl pyrrolidone and sodium starch glycolate. The filler may be
10 one or more of microcrystalline cellulose, lactose, starch, and cross-linked polyvinyl pyrrolidone. The binder may be one or more of hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, and polyvinyl pyrrolidone. The glidant may be one or more of starch, talc, stearates, and colloidal silicon dioxide. The lubricant may be one or more of stearic acid, talc, sodium stearyl fumarate, mineral oil, and magnesium stearate.

15 The composition may be in the form of one or more of granules, tablets, capsules, dry syrup, suspension, and sachets. The composition may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid, and losartan. The fenofibrate and the one or more active ingredients may be combined in a single pharmaceutical composition.

20 In another general aspect, an oral pharmaceutical composition includes from about 20% w/w to about 45% w/w of micronized fenofibrate, from about 10% w/w to about 45% w/w of one or more hydrophilic polymers, from about 0.5% w/w to about 3.0% w/w of one or more surfactants, and from about 20% w/w to about 60% w/w of inert hydro-insoluble carrier.

25 Embodiments of the composition may include one or more of the features described above or the following features. For example, the micronized fenofibrate may have a size less than or equal to about 20 microns.

The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch. The hydrophilic polymer may be one or more
30 of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol and gelatin. The surfactant may be one or more of sodium lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene

sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids and propylene glycol laurate. The composition may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan.

5 The composition may have a dissolution of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes, and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

10 In another general aspect there is provided a process for preparing a pharmaceutical composition of fenofibrate having an improved dissolution profile. The process includes mixing micronized fenofibrate, one or more hydrophilic polymers and one or more surfactants to obtain a solution or dispersion, and layering the solution or dispersion onto a hydro-insoluble carrier to obtain granulates.

15 Embodiments of the process may include one or more of the features described above or the following features. For example, the process may further include mixing the granulates with one or more pharmaceutically acceptable excipients selected from the group that includes one or more of fillers, binders, disintegrants, lubricants, glidants, colorants, lubricants, wetting agents, buffers, and flavoring agents to obtain a mixture.

20 The process may further include processing the granulates to obtain the pharmaceutical composition, wherein the pharmaceutical composition has a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium
25 constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

 The process may further include processing the mixture to obtain the pharmaceutical composition, wherein the pharmaceutical composition has a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20
30 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

5 The hydro-insoluble carrier may be selected from the group that includes one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch, and may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

10 The hydrophilic polymer may be selected from the group that includes one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol and gelatin, and may be present in an amount of from about 10% w/w to about 45% w/w of the composition.

15 The surfactant may be selected from the group that includes one or more of sodium lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about 0.5% w/w to about 3.0% w/w of the composition.

The composition may be processed to be in the form of one or more of granules, tablets, capsules, dry syrup, suspensions or sachets.

20 The process may further include adding one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan.

25 In another general aspect there is provided a method of treating one or more of hyperlipidemia, hypercholesterolemia and hypertriglyceridemia, the method including administering an oral pharmaceutical composition of fenofibrate that includes an inert hydro-insoluble carrier with at least one layer containing fenofibrate in a micronized form, one or more hydrophilic polymers and one or more surfactants.

Embodiments of the treatment method may include one or more of the features described above or the following features. For example, the composition may further include one or more outer phases or layers. The two or more outer phases or layers may include one or more of fenofibrate in a micronized form, a hydrophilic polymer, and a surfactant.

The micronized fenofibrate may have a size less than or equal to about 20 microns, and may be present in an amount of from about 20% w/w to about 45% w/w of the composition.

5 The hydro-insoluble carrier may be one or more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch, and may be present in an amount of from about 20% w/w to about 60% w/w of the composition.

The hydrophilic polymer may be one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose, polyvinyl alcohol, and gelatin, and may be present in an amount of from about 10% w/w to about 45% w/w of the composition.

10 The surfactant may be one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol laurate. The surfactant may be present in an amount of from about 0.5% w/w to about 3.0% w/w of the composition.

15 The composition may have a dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

20 The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

DETAILED DESCRIPTION OF THE INVENTION

25 Drug efficacy depends in part upon its bioavailability (i.e., absorption into the systemic circulation) to the patient to whom the drug is administered. For drugs that are hydrophobic or poorly soluble in water, increased wettability upon exposure to biological fluids can be an objective for those formulating and manufacturing these agents. Fenofibrate is practically insoluble in water. This insolubility characteristic causes fenofibrate to exhibit a low rate of dissolution in aqueous media, e.g., gastrointestinal fluids, which results in
30 inadequate bioavailability after oral ingestion.

In order to make a pharmaceutical composition of fenofibrate that will provide maximum bioavailability, it is necessary to incorporate into the composition a feature that increases the rate of dissolution of the drug in gastrointestinal fluids. Several ways of increasing the rate of dissolution of drugs having low solubility in water are known in the art.

5 One approach is micronization of the drug whose solubility is insufficient. In this approach, the drug is milled to fine particles, typically having a mean diameter of under about 15 microns. A second approach is to include a surfactant in the composition. For the drug fenofibrate, neither micronization alone nor use of a surfactant alone provides maximum bioavailability. As disclosed above, Laboratories Fournier's patents, U.S. Patent Nos.

10 6,074,670 and 6,277,405 disclose that by spraying a suspension of the micronized active onto a hydro-soluble carrier, they can increase the bioavailability of fenofibrate.

We have unexpectedly found that contrary to the disclosure of the above prior art, the use of a hydro-soluble carrier is not a prerequisite for improving the bioavailability of fenofibrate and that it is possible to make fenofibrate formulations having improved solubility

15 and bioavailability by spraying a suspension of fenofibrate onto an inert hydro-insoluble carrier. The spraying can be performed such that one or more layers or phases of the fenofibrate are formed on the hydro-insoluble carrier. The composition thus obtained was found to possess a release profile similar to that reported in U.S. Patent Nos. 6,074,670 and 6,277,405.

20 Micronized fenofibrate as described herein relates to fenofibrate particles having a mean particle size of less than about 20 μm . Particularly, the mean particle size is less than about 10 μm . The compositions generally include from about 20% to about 45% by weight of micronized fenofibrate.

Size reduction, or micronization, may be carried out using any of the conventionally

25 known mills, such as a ball mill, air jet mill, impact mill, etc. Air jet milling is particularly well suited for this application as it is a well proven technique that consistently produces particles of a size less than about 20 microns. Primary advantages of air jet milling are that the predominant particle size reduction occurs through particle to particle collisions, there is limited particle size reduction that results from metal to product contact, and there is no

30 generation of heat that can adversely affect the particles being micronized.

The process of air jet milling involves exposing the material to be micronized to streams of compressed air or gas. Particles in the fluidized bed created by the gas streams are

accelerated towards the center of the mill and collide with the slower moving particles. These collisions break the particles into smaller particles, thereby micronizing the particles. The air jet mills operate by applying opposing air flows and centrifugal forces. By balancing the two forces, desired particle size and fines can be separated.

5 As used herein, the expression "inert hydro-insoluble carrier" means any pharmaceutically acceptable excipient that is water insoluble and inert. Examples of inert, water insoluble carriers include, but are not limited to, microcrystalline cellulose, dicalcium phosphate, partially pregelatinized starch, and other suitable synthetic and organic polymers. The hydro-insoluble carrier may be present in an amount from about 20% w/w to about 60%
10 w/w of the total weight of the pharmaceutical composition.

 The term "hydrophilic polymer" according to this invention should be taken to mean any high molecular weight substance having sufficient affinity towards water. Examples of such polymers include but are not limited to hydroxymethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, gelatin
15 and their mixtures. The hydrophilic polymer may be present in an amount from about 10% w/w to about 45% w/w of the total weight of the pharmaceutical composition.

 A surfactant according to this invention may be amphoteric, non-ionic, cationic, or anionic. Examples of such surfactants include but are not limited to sodium lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters of polyoxyethylene
20 sorbitan, polyethylene glycol laurate, lecithins, propylene glycol alginate, bile acids, phospholipids, propylene glycol laurate, etc. Mixtures of surfactants are also suitable. The surfactant may be present in an amount from about 0.5% w/w to about 3% w/w by weight of the total weight of the pharmaceutical composition.

 One suitable process for making the improved bioavailability dosage form includes
25 spraying a suspension of the active ingredient in micronized form and a hydrophilic polymer onto a hydro-insoluble carrier resulting in a pharmaceutical composition of the active ingredient (e.g., fenofibrate) with an improved dissolution profile.

 The compositions having improved bioavailability additionally may contain other excipients that are used in the pharmaceutical and chemical fields and are compatible with the
30 active ingredient (e.g., fenofibrate), such as disintegrants, glidants, lubricants, binders, fillers, pigments, wetting agents, buffers, etc.

Examples of disintegrants used in the compositions include but are not limited to those known in the art, such as croscarmellose sodium, cross-linked polyvinyl pyrrolidone, sodium starch glycolate, and mixtures thereof. Example of glidants used in the compositions include but are not limited to those known in the art, such as starch, talc, stearates, colloidal silica, and mixtures thereof. Examples of lubricants used in the compositions include but are not limited to those known in the art, such as stearic acid, talc, magnesium stearate, sodium stearyl fumarate, mineral oil and the like, and mixtures thereof. Examples of binders used in the compositions include but are not limited to those known in the art, such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, polyvinyl pyrrolidone and the like, and mixtures thereof. Examples of fillers used in the compositions include but are not limited to those known in the art, such as microcrystalline cellulose, lactose, starch, cross-linked polyvinyl pyrrolidone, etc., and mixtures thereof.

The compositions in accordance with the present inventions may be filled into capsules, formulated as dry syrups, suspensions or mixed with other pharmaceutically acceptable excipients and compressed into tablets. The tablets may further be coated.

Examples of some film forming polymers that can be used for the coating used to coat the compositions include but are not limited to those known in the art, such as cellulose derivatives (hydroxypropyl methylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and their derivatives), acrylic and methacrylic copolymers of different molecular weights, and mixtures thereof.

The compositions generally include, based on the total composition weight, an inert hydro-insoluble carrier representing about 20% to about 60% by weight, micronized fenofibrate representing from about 20% to about 45% by weight, one or more hydrophilic polymers representing from about 10% to about 45% by weight, and one or more surfactants representing about 0.5% to about 3% by weight.

According to one specific embodiment, a process for preparing a pharmaceutical composition of fenofibrate with improved dissolution profile includes the following steps:

- a. mixing micronized fenofibrate, one or more hydrophilic polymers, and one or more surfactants to obtain a solution or dispersion;
- b. layering the solution or dispersion onto a hydro-insoluble carrier to obtain granulates;

c. mixing the granulates with one or more pharmaceutically acceptable excipients selected from the group that includes fillers, binders, disintegrants, lubricants, glidants, colorants and flavoring agents to obtain a mixture; and

5 d. processing the granulates or mixture to obtain a pharmaceutical composition having a dissolution profile of at least about 10% in 5 minutes, about 20% in 10 minutes, about 50% in 20 minutes and about 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to European Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium lauryl sulphate.

10 The oral pharmaceutical compositions of fenofibrate described herein may be used for the treatment of hyperlipidemia, hypercholesterolemia, and/or hypertriglyceridemia. The pharmaceutical compositions may further include one or more of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin, niacin, folic acid and losartan. The fenofibrate and the one or more of the active ingredients may be combined
15 in a single pharmaceutical composition.

The following examples further exemplify the inventions and are not intended to limit the scope of the inventions.

EXAMPLE 1

Ingredients	Percent w/w of composition (%)
Micronized fenofibrate	23
Pregelatinized starch (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose	14
Cross-linked polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Process:

Sodium lauryl sulphate was dissolved in water and then the micronized fenofibrate was added to the dissolved sodium lauryl sulphate while stirring continuously. Following this addition, polyvinylpyrrolidone was added while still agitating to form a dispersion. This dispersion was sprayed onto the pregelatinized starch in Glatt process technology using bottom spray. The granulate thus obtained was mixed with cross-linked polyvinyl pyrrolidone, colloidal silicon dioxide, and sodium stearyl fumarate and compressed to form tablets. The tablets thus obtained were film coated.

Tablets of this example 1, herein referred to as tablet I, were compared with Fournier's marketed tablets, herein referred to as tablet II, the formulation having been made in accordance with the invention disclosed in U.S. Patent No. 6,277,405 for dissolution rate. The corresponding release profiles are provided in Table 1.

Table 1: Release profile of tablets prepared according to Example 1 and Fournier's marketed tablets (II) in 1000 ml water/rotating blade method (European Pharmacopoeia)/37°C/75 rpm

Time (Minutes)	Percent Drug Released (%)	
	Tablet I	Tablet II
10	86	84
20	100	98
30	101	100

From the results, it is evident that over 95% drug is released in 20 minutes in both formulations and that tablets I and II show substantially similar dissolution profiles. The formulation containing the hydro-insoluble core also gives a dissolution profile that is similar to that disclosed in U.S. Patent No. 6,277,405, i.e., 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes.

EXAMPLE 2

Ingredients	Percent w/w of composition (%)
Micronized fenofibrate	23
Microcrystalline cellulose (core)	39.5
Polyvinyl pyrrolidone	17
Sodium lauryl sulphate	1
Microcrystalline cellulose (extra granular)	14
Cross-linked polyvinyl pyrrolidone	4
Colloidal silicon dioxide	0.5
Sodium stearyl fumarate	1

Process:

A fenofibrate (micronized) suspension was prepared in a similar way to that of Example 1 and sprayed onto microcrystalline cellulose powder in Glatt process technology using bottom spray to form a granulate. The granulate thus prepared was mixed with a cross-linked polyvinyl pyrrolidone, colloidal silicon dioxide and sodium stearyl fumarate and compressed to form tablets. These tablets were film coated.

The tablets of this example were subjected to dissolution studies using the rotating blade method at 50 rpm according to European Pharmacopoeia in a dissolution medium constituted by 1000 ml water containing 0.025M sodium lauryl sulphate at 37°C. The results are provided in Table 2.

Table 2: Release profile of tablets prepared according to Example 2 in 1000 ml water/rotating blade method (European Pharmacopoeia)/37°C/50 rpm

Time (minutes)	Percent Drug Released (%)
10	53.0
20	75.1
30	85.2
45	91.0

The results indicate that although the speed was reduced from 75 rpm to 50 rpm, more than 90% of the drug is still released in 45 minutes. Thus, it can be concluded that the formulation containing hydro-insoluble core gives a similar dissolution profile to that claimed
5 in U.S. Patent No. 6,277,405 even at a slower rotation speed.

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Further, it is contemplated that any single feature or any combination of optional features of the inventive
10 variations described herein may be specifically excluded from the claimed inventions and be so described as a negative limitation. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

WE CLAIM:

- 1 1. An oral pharmaceutical composition of fenofibrate comprising an inert hydro-
2 insoluble carrier having one or more one layers comprising fenofibrate in a
3 micronized form, a hydrophilic polymer, and a surfactant.
- 1 2. The composition of claim 1, further comprising two or more outer phases or layers.
- 1 3. The composition of claim 2, wherein the two or more outer phases or layers comprise
2 one or more of fenofibrate in a micronized form, a hydrophilic polymer, and a
3 surfactant.
- 1 4. The composition of claim 1, wherein the micronized fenofibrate has a size less than or
2 equal to about 20 microns.
- 1 5. The composition of claim 1, wherein the micronized fenofibrate has a size less than or
2 equal to about 10 microns.
- 1 6. The composition of claim 1, wherein the micronized fenofibrate comprises an amount
2 of from about 20% w/w to about 45% w/w of the composition.
- 1 7. The composition of claim 1, wherein the hydro-insoluble carrier comprises one or
2 more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch.
- 1 8. The composition of claim 1, wherein the hydro-insoluble carrier comprises an amount
2 of from about 20% w/w to about 60% w/w of the composition.
- 1 9. The composition of claim 1, wherein the hydrophilic polymer comprises one or more
2 of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose,
3 polyvinyl alcohol, and gelatin.
- 1 10. The composition of claim 1, wherein the hydrophilic polymer comprises an amount of
2 from about 10% w/w to about 45% w/w of the composition.
- 1 11. The composition of claim 1, wherein the surfactant comprises one or more of sodium
2 lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters
3 of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol
4 alginate, bile acids, phospholipids, and propylene glycol laurate.
- 1 12. The composition of claim 1, wherein the surfactant comprises an amount of from
2 about 0.5% w/w to about 3.0% w/w of the composition.

- 1 13. The composition of claim 1, wherein the composition further comprises one or more
2 pharmaceutically acceptable excipients comprising disintegrants, binders, fillers,
3 glidants, lubricants, colorants, wetting agents, buffers, and coatings.
- 1 14. The composition of claim 13, wherein the disintegrant comprises one or more of
2 croscarmellose sodium, cross-linked polyvinyl pyrrolidone and sodium starch
3 glycolate.
- 1 15. The composition of claim 13, wherein the filler comprises one or more of
2 microcrystalline cellulose, lactose, starch, and cross-linked polyvinyl pyrrolidone.
- 1 16. The composition of claim 13, wherein the binder comprises one or more of
2 hydroxypropyl methylcellulose, hydroxypropyl cellulose, gelatin, and polyvinyl
3 pyrrolidone.
- 1 17. The composition of claim 13, wherein the glidant comprises one or more of starch,
2 talc, stearates, and colloidal silicon dioxide.
- 1 18. The composition of claim 13, wherein the lubricant comprises one or more of stearic
2 acid, talc, sodium stearyl fumarate, mineral oil, and magnesium stearate.
- 1 19. The composition of claim 1, wherein the composition comprises one or more of
2 granules, tablets, capsules, dry syrup, suspension, and sachets.
- 1 20. The composition of claim 1, wherein the composition further comprises one or more
2 of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin,
3 rosuvastatin, metformin, niacin, folic acid, and losartan.
- 1 21. The composition of claim 20, wherein the fenofibrate and the one or more active
2 ingredients are combined in a single pharmaceutical composition.
- 1 22. The composition of claim 1, wherein the composition has a dissolution of at least
2 about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20
3 minutes, and about 75% in about 30 minutes, as measured using the rotating blade
4 method at 75 rpm according to the European Pharmacopoeia in a dissolution medium
5 constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium
6 lauryl sulphate.
- 1 23. An oral pharmaceutical composition comprising from about 20% w/w to about 45%
2 w/w of micronized fenofibrate, from about 10% w/w to about 45% w/w of one or
3 more hydrophilic polymers, from about 0.5% w/w to about 3.0% w/w of one or more

- 4 surfactants, and from about 20% w/w to about 60% w/w of one or more inert hydro-
5 insoluble carriers.
- 1 24. The composition of claim 23, wherein the micronized fenofibrate has a size less than
2 or equal to about 20 microns.
- 1 25. The composition of claim 23 wherein the hydro-insoluble carrier comprises one or
2 more of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch.
- 1 26. The composition of claim 23, wherein the hydrophilic polymer comprises one or more
2 of polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose,
3 polyvinyl alcohol and gelatin.
- 1 27. The composition of claim 23, wherein the surfactant comprises one or more of sodium
2 lauryl sulphate, monoleate, monolaurate, monopalmitate, monostearate or other esters
3 of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol
4 alginate, bile acids, phospholipids and propylene glycol laurate.
- 1 28. The composition of claim 23, wherein the composition further comprises one or more
2 of simvastatin, lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin,
3 rosuvastatin, metformin, niacin, folic acid and losartan.
- 1 29. The composition of claim 23, wherein the composition has a dissolution of at least
2 about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20
3 minutes, and about 75% in about 30 minutes, as measured using the rotating blade
4 method at 75 rpm according to the European Pharmacopoeia in a dissolution medium
5 constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium
6 lauryl sulphate.
- 1 30. A process for preparing a pharmaceutical composition of fenofibrate and having an
2 improved dissolution profile, the process comprising:
- 3 a. mixing micronized fenofibrate, one or more hydrophilic polymers and one or
4 more surfactants to obtain a solution or dispersion, and
- 5 b. layering the solution or dispersion onto a hydro-insoluble carrier to obtain
6 granulates.
- 1 31. The process of claim 30, further comprising mixing the granulates with one or more
2 pharmaceutically acceptable excipients selected from the group comprising one or

- 3 more of fillers, binders, disintegrants, lubricants, glidants, colorants, lubricants,
4 wetting agents, buffers, and flavoring agents to obtain a mixture.
- 1 32. The process of claim 30, further comprising processing the granulates to obtain the
2 pharmaceutical composition, wherein the pharmaceutical composition has a
3 dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10
4 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as
5 measured using the rotating blade method at 75 rpm according to the European
6 Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of
7 Polysorbate 80 or with 0.025M sodium lauryl sulphate.
- 1 33. The process of claim 31, further comprising processing the mixture to obtain the
2 pharmaceutical composition, wherein the pharmaceutical composition has a
3 dissolution profile of at least about 10% in about 5 minutes, about 20% in about 10
4 minutes, about 50% in about 20 minutes and about 75% in about 30 minutes, as
5 measured using the rotating blade method at 75 rpm according to the European
6 Pharmacopoeia in a dissolution medium constituted by water with 2% by weight of
7 Polysorbate 80 or with 0.025M sodium lauryl sulphate.
- 1 34. The process of claim 30, wherein the micronized fenofibrate has a size less than or
2 equal to about 20 microns.
- 1 35. The process of claim 30, wherein the micronized fenofibrate comprises an amount of
2 from about 20% w/w to about 45% w/w of the composition.
- 1 36. The process of claim 30, wherein the hydro-insoluble carrier is selected from the
2 group comprising one or more of microcrystalline cellulose, dicalcium phosphate and
3 pregelatinized starch.
- 1 37. The process of claim 30, wherein the hydro-insoluble carrier comprises an amount of
2 from about 20% w/w to about 60% w/w of the composition.
- 1 38. The process of claim 30, wherein the hydrophilic polymer is selected from the group
2 comprising one or more of polyvinyl pyrrolidone, hydroxy propyl cellulose,
3 hydroxypropyl methylcellulose, polyvinyl alcohol and gelatin.
- 1 39. The process of claim 30, wherein the hydrophilic polymer comprises an amount of
2 from about 10% w/w to about 45% w/w of the composition.

- 1 40. The process of claim 30, wherein the surfactant is selected from the group comprising
2 one or more of sodium lauryl sulphate, monoleate, monolaurate, monopalmitate,
3 monostearate or other esters of polyoxyethylene sorbitan, polyethylene glycol laurate,
4 lecithins, propylene glycol alginate, bile acids, phospholipids, and propylene glycol
5 laurate.
- 1 41. The process of claim 30, wherein the surfactant comprises an amount of from about
2 0.5% w/w to about 3.0% w/w of the composition.
- 1 42. The process of claim 30, wherein the composition comprises one or more of granules,
2 tablets, capsules, dry syrup, suspensions or sachets.
- 1 43. The process of claim 30, further comprises adding one or more of simvastatin,
2 lovastatin, atorvastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, metformin,
3 niacin, folic acid and losartan.
- 1 44. A method of treating one or more of hyperlipidemia, hypercholesterolemia and
2 hypertriglyceridemia, the method comprising administering an oral pharmaceutical
3 composition of fenofibrate comprising an inert hydro-insoluble carrier with at least
4 one layer containing fenofibrate in a micronized form, one or more hydrophilic
5 polymers and one or more surfactants.
- 1 45. The method of claim 44, wherein the composition further comprises one or more
2 outer phases or layers.
- 1 46. The method of claim 45, wherein the two or more outer phases or layers comprise one
2 or more of fenofibrate in a micronized form, one or more hydrophilic polymers, and
3 one or more surfactants.
- 1 47. The method of claim 44, wherein the micronized fenofibrate has a size less than or
2 equal to about 20 microns.
- 1 48. The method of claim 44, wherein the micronized fenofibrate comprises an amount of
2 from about 20% w/w to about 45% w/w of the composition.
- 1 49. The method of claim 44, wherein the hydro-insoluble carrier comprises one or more
2 of microcrystalline cellulose, dicalcium phosphate and pregelatinized starch.
- 1 50. The method of claim 44, wherein the hydro-insoluble carrier comprises an amount of
2 from about 20% w/w to about 60% w/w of the composition.

- 1 51. The method of claim 44, wherein the hydrophilic polymer comprises one or more of
2 polyvinyl pyrrolidone, hydroxy propyl cellulose, hydroxypropyl methylcellulose,
3 polyvinyl alcohol, and gelatin.
- 1 52. The method of claim 44, wherein the hydrophilic polymer comprises an amount of
2 from about 10% w/w to about 45% w/w of the composition.
- 1 53. The method of claim 44, wherein the surfactant comprises one or more of sodium
2 lauryl sulphate, monooleate, monolaurate, monopalmitate, monostearate or other esters
3 of polyoxyethylene sorbitan, polyethylene glycol laurate, lecithins, propylene glycol
4 alginate, bile acids, phospholipids, and propylene glycol laurate.
- 1 54. The method of claim 44, wherein the surfactant comprises an amount of from about
2 0.5% w/w to about 3.0% w/w of the composition.
- 1 55. The method of claim 44, wherein the composition has a dissolution profile of at least
2 about 10% in about 5 minutes, about 20% in about 10 minutes, about 50% in about 20
3 minutes and about 75% in about 30 minutes, as measured using the rotating blade
4 method at 75 rpm according to the European Pharmacopoeia in a dissolution medium
5 constituted by water with 2% by weight of Polysorbate 80 or with 0.025M sodium
6 lauryl sulphate.

Inte	Application No
PCT/IB	03/04162

According to International Patent Classification (IPC) or to both national classification and IPC

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 819 720 A (FOURNIER SA LAB) 26 July 2002 (2002-07-26) page 5, line 10-22; example 1 ---	23-29
X	WO 02 11699 A (IMPAX-LAB INC) 14 February 2002 (2002-02-14) page 8, line 27 -page 9, line 24 tables 1,7 A page 3, line 2-22 ---	23-29
A	---	1-22, 30-55
A	FR 2 795 961 A (ETHYPHARM LAB PROD ETHIQUES) 12 January 2001 (2001-01-12) page 3, line 3-12 page 4, line 19-27 example 1 --- --/--	1-55

X

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *& document member of the same patent family

Date of the actual completion of the international search

13 January 2004

Date of mailing of the international search report

22/01/2004

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Vermeulen, S

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/IB 03/04162

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 494 112 A (LARUELLE CLAUDE) 21 May 1982 (1982-05-21) page 1, line 27-40 page 2, line 11-17 page 2, line 40 -page 3, line 17 ---	1-55
A	US 6 074 670 A (STAMM ANDRE ET AL) 13 June 2000 (2000-06-13) cited in the application column 3, line 13-45; example 1 ---	1-55
A	WO 00 16749 A (TOSELLI DOMINIQUE ;CLL PHARMA (FR); GIMET RENE (FR); LARUELLE CLAU) 30 March 2000 (2000-03-30) page 4, line 29 -page 5, line 27 examples 1,2 ---	1-55
E	WO 03 082247 A (ROSENBERGER VERED ;TEVA PHARMA (IL); DRABKIN ANNA (IL); LERNER ITZ) 9 October 2003 (2003-10-09) page 3, line 6-16 page 6, line 27 example 2 -----	1-55

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 03/04162

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 44-55 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/IB 03/04162

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
FR 2819720	A	26-07-2002	FR 2819720 A1	26-07-2002
			CA 2435714 A1	25-07-2002
			EP 1353663 A1	22-10-2003
			WO 02056881 A1	25-07-2002
WO 0211699	A	14-02-2002	US 6531158 B1	11-03-2003
			AU 8076401 A	18-02-2002
			WO 0211699 A1	14-02-2002
			US 2003138496 A1	24-07-2003
FR 2795961	A	12-01-2001	FR 2795961 A1	12-01-2001
			AU 6296000 A	30-01-2001
			BG 106280 A	30-08-2002
			BR 0012335 A	19-03-2002
			CA 2377909 A1	18-01-2001
			CN 1360499 T	24-07-2002
			CZ 20020002 A3	15-05-2002
			EE 200200011 A	17-02-2003
			EP 1194140 A1	10-04-2002
			WO 0103693 A1	18-01-2001
			HR 20020111 A1	30-04-2003
			HU 0202338 A2	28-10-2002
			JP 2003504331 T	04-02-2003
			NO 20020014 A	04-03-2002
			NZ 516416 A	31-10-2003
			SK 152002 A3	02-07-2002
			TR 200200008 T2	21-06-2002
			ZA 200200169 A	09-07-2002
FR 2494112	A	21-05-1982	FR 2494112 A1	21-05-1982
			AT 387517 B	10-02-1989
			AT 906481 A	15-07-1988
			BE 891129 A1	17-05-1982
			DE 3152519 T0	29-12-1983
			EP 0065531 A1	01-12-1982
			WO 8201649 A1	27-05-1982
			IT 1144948 B	29-10-1986
			NL 8120434 T	01-10-1982
US 6074670	A	13-06-2000	FR 2758459 A1	24-07-1998
			AT 233556 T	15-03-2003
			AU 731964 B2	05-04-2001
			AU 5336798 A	07-08-1998
			BR 9806738 A	29-02-2000
			CA 2219475 A1	17-07-1998
			CA 2372561 A1	17-07-1998
			CA 2372576 A1	17-07-1998
			CZ 9902535 A3	17-11-1999
			DE 69811855 D1	10-04-2003
			DE 69811855 T2	18-12-2003
			DK 952829 T3	23-06-2003
			EE 9900296 A	15-02-2000
			EP 1273293 A1	08-01-2003
			EP 1273294 A1	08-01-2003
			EP 1275387 A1	15-01-2003
			EP 0952829 A1	03-11-1999
			HK 1023071 A1	15-08-2003
			HU 0000808 A2	28-12-2000

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/IB 03/04162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6074670	A	WO 9831361 A1	23-07-1998
		ID 22528 A	28-10-1999
		JP 2001511156 T	07-08-2001
		NO 993519 A	16-09-1999
		NZ 336462 A	29-09-2000
		PL 334748 A1	13-03-2000
		PT 952829 T	31-07-2003
		RU 2196580 C2	20-01-2003
		SK 96299 A3	14-08-2000
		TR 9901660 T2	21-09-1999
		US 2002114839 A1	22-08-2002
		US 2002168413 A1	14-11-2002
		US 2003104051 A1	05-06-2003
		US 2003104060 A1	05-06-2003
		US 6277405 B1	21-08-2001
		US 2002009496 A1	24-01-2002
		ZA 9800324 A	12-08-1998
WO 0016749	A 30-03-2000	FR 2783421 A1	24-03-2000
		AT 230979 T	15-02-2003
		AU 5523599 A	10-04-2000
		BR 9913782 A	05-06-2001
		CA 2342742 A1	30-03-2000
		CZ 20010979 A3	15-08-2001
		DE 69904954 D1	20-02-2003
		EP 1112064 A1	04-07-2001
		ES 2190819 T3	16-08-2003
		WO 0016749 A1	30-03-2000
		JP 2002526438 T	20-08-2002
		PL 346714 A1	25-02-2002
		SK 3552001 A3	11-09-2001
		ZA 200101894 A	07-01-2003
WO 03082247	A 09-10-2003	WO 03082247 A2	09-10-2003
		US 2003224059 A1	04-12-2003